Attach Paper #9

L Number	Hits	Search Text	DB	Time stamp
1	25	"5474935"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:36
7	0	chattorjee-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:36
13	1407	chatterjee-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:36
19	596	wong-k$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:37
25	839	wong-c$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:37
31	0	fisher-adams-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:37
37	7759	fisher-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:38
43	11029	adams-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:38
44	21609	chatterjee-$.in. or wong-k$.in. or wong-c$.in. or fisher-$.in. or adams-$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:38
50	23	(chatterjee-$.in. or wong-k$.in. or wong-c$.in. or fisher-$.in. or adams-$.in.) and aav	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:39
56	29	(chatterjee-$.in. or wong-k$.in. or wong-c$.in. or fisher-$.in. or adams-$.in.) and (aav or (adeno-associated or adenoassociated or (adeno adj3 associated)))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:44
62	3	((chatterjee-$.in. or wong-k$.in. or wong-c$.in. or fisher-$.in. or adams-$.in.) and (aav or (adeno-associated or adenoassociated or (adeno adj3 associated)))) and (cd34$3 or (hematopoietic with stem))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:44
68	263	(aav or (adeno-associated or adenoassociated or (adeno adj3 associated))) and (cd34$3 or (hematopoietic with stem))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:44
74	14	((aav or (adeno-associated or adenoassociated or (adeno adj3 associated))) and (cd34$3 or (hematopoietic with stem))) and (g0 or (stationary with phase))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2001/07/13 23:45

Attach Paper #9

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      (FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001)

      FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 23:18:09 ON 13 JUL 2001
L1         20055 S (CHATTERJEE, ?)/IN,AU
L2         85570 S (WONG, ?)/IN,AU
L3          6617 S (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS,
G?)
L4        112099 S L1 OR L2 OR L3
L5            13 S L1 AND L2 AND L3
L6             7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)
L7           228 S L4 AND (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L8             8 S L7 AND G0
L9             4 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)
L10          124 S G0 (S) (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L11            1 S L10 AND (AAV OR (ADENOASSOCIATED (3W) VIRUS) OR
(ADENO-ASSOCI
L12            0 S L10 AND ADENOVIRUS
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Trying 3106016892...Open

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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Dec 17  The CA Lexicon available in the CAPLUS and CA files
 NEWS  3  Feb 06  Engineering Information Encompass files have new names
 NEWS  4  Feb 16  TOXLINE no longer being updated
 NEWS  5  Apr 23  Search Derwent WPINDEX by chemical structure
 NEWS  6  Apr 23  PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
 NEWS  7  May 07  DGENE Reload
 NEWS  8  Jun 20  Published patent applications (A1) are now in USPATFULL
 NEWS  9  JUL 13  New SDI alert frequency now available in Derwent's
                  DPWI and DPCI

 NEWS EXPRESS  July 11 CURRENT WINDOWS VERSION IS V6.0b,
               CURRENT MACINTOSH VERSION IS V5.0C (ENG) AND V5.0JB (JP),
               AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2001
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FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001

=> file medline embase biosis caplus

COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
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FULL ESTIMATED COST                                       0.15       0.15

FILE 'MEDLINE' ENTERED AT 23:18:09 ON 13 JUL 2001

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=> s (chatterjee, ?)/in,au

'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L1       20055 (CHATTERJEE, ?)/IN,AU

=> s (wong, ?)/in,au

'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L2       85570 (WONG, ?)/IN,AU

=> s (fisher-adams, g?)/in,au or (fisher, g?)/in,au or (adams, g?)/in,au

'IN' IS NOT A VALID FIELD CODE
'IN' IS NOT A VALID FIELD CODE
L3        6617 (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS,
G?)/IN
               ,AU

=> s l1 or l2 or l3

L4      112099 L1 OR L2 OR L3

=> s l1 and l2 and l3

L5           13 L1 AND L2 AND L3

=> duplicate remove l5

DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n

PROCESSING COMPLETED FOR L5
L6             7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)

=> d ibib ab 16 1-7


L6   ANSWER 1 OF 7  MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:   1999168976     MEDLINE
DOCUMENT NUMBER:    99168976   PubMed ID: 10068661
TITLE:              Transduction of primitive human marrow and cord
                    blood-derived hematopoietic progenitor cells with
                    adeno-associated virus vectors.
AUTHOR:             Chatterjee S; Li W; Wong C A;
                    Fisher-Adams G; Lu D; Guha M; Macer J A; Forman S
                    J; Wong K K Jr
CORPORATE SOURCE:   Division of Pediatrics, Department of Hematology and Bone
                    Marrow Transplantation, City of Hope National Medical
                    Center, Duarte, CA, USA.. schatterjee@coh.org
CONTRACT NUMBER:    AI-RO140001 (NIAID)
                    AI-U1938592 (NIAID)
                    CA-RO171947 (NCI)
                    +
SOURCE:             BLOOD, (1999 Mar 15) 93 (6) 1882-94.
                    Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
```

ENTRY MONTH: 199[redacted]3
ENTRY DATE: Ent[redacted]ed STN: 19990413
Last Updated on STN: 19990413
Entered Medline: 19990330

AB We evaluated the capacity of adeno-associated virus (AAV) vectors to transduce primitive human myeloid progenitor cells derived from marrow and cord blood in long-term cultures and long-term culture-initiating cell (LTC-IC) assays. Single-colony analyses showed that AAV vectors transduced CD34(+) and CD34(+)38(-) clonogenic cells in long-term culture. Gene transfer was readily observed in LTC-ICs derived from 5-, 8-, and 10-week cultures. Recombinant AAV (rAAV) transduction was observed in every donor analyzed, although a wide range of gene transfer frequencies (5% to 100%) was noted. AAV transduction of LTC-ICs was stable, with week-8 and -10 LTC-ICs showing comparable or better transduction relative to week-5 LTC-ICs. Fluorescence in situ hybridization (FISH) analyses performed to determine the fate of AAV vectors in transduced cells showed that 9% to 28% of CD34(+) and CD34(+)38(-) cells showed stable vector integration as evidenced by chromosome-associated signals in metaphase spreads. Comparisons of interphase and metaphase FISH suggested that a fraction of cells also contained episomal vector at early time points after transduction. Despite the apparent loss of the episomal forms with continued culture, the number of metaphases containing integrated vector genomes remained stable long term. Transgene transcription and placental alkaline phosphatase (PLAP) expression was observed in CD34(+), CD34(+)38(-) LTC-ICs in the absence of selective pressure. These results suggest that primitive myeloid progenitors are amenable to genetic modification with AAV vectors.

L6 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:16582 CAPLUS
DOCUMENT NUMBER: 130:232866
TITLE: Parvovirus vectors for the gene therapy of cancer
AUTHOR(S): **Wong, K. K., Jr.**; Shaughnessy, Elizabeth; Lu, Di; **Fisher-Adams, Grace**; **Chatterjee, Saswati**
CORPORATE SOURCE: Department of Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte, CA, 91010, USA
SOURCE: Gene Ther. Cancer (1999), 95-111, 1 plate.
Editor(s): Lattime, Edmund C.; Gerson, Stanton L. Academic: San Diego, Calif.
CODEN: 67DQAI
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review, with 180 refs., covering the basic biol. of parvoviruses in relation to development of genetic vectors, potential advantages and disadvantages of parvovirus vectors, and application for the treatment of cancer.

REFERENCE COUNT: 180
REFERENCE(S):
(1) Alexander, I; J Virol 1994, V68, P8282 CAPLUS
(2) Ali, R; Hum Mol Genet 1996, V5, P591 CAPLUS
(6) Avalosse, B; J Virol Methods 1996, V62, P179 CAPLUS
(9) Baudard, M; Hum Gene Ther 1996, V7, P1309 CAPLUS
(10) Berns, K; Adv Virus Res 1987, V32, P243 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1998:67368 BIOSIS
DOCUMENT NUMBER: PREV199800067368
TITLE: Gene transfer into multipotential self renewing murine hematopoietic progenitor cells by AAV vectors.

AUTHOR(S): Ro[redacted]rough, E.; Shaughessy, E. A.; L[redacted] W.; Li, L.-J.; **Fish[redacted]Adams, G.**; Podsakoff, G. M.; [redacted] **Chatterjee, S.**; **Wong, K. K., Jr.**

CORPORATE SOURCE: City Hope Natl. Med. Cent., Duarte, CA USA

SOURCE: Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 241A.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology San Diego, California, USA December 5-9, 1997
The American Society of Hematology
. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

L6 ANSWER 4 OF 7 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 96289498 MEDLINE

DOCUMENT NUMBER: 96289498 PubMed ID: 8695797

TITLE: Integration of adeno-associated virus vectors in CD34+ human hematopoietic progenitor cells after transduction.

AUTHOR: **Fisher-Adams G**; **Wong K K Jr**; Podsakoff G; Forman S J; **Chatterjee S**

CORPORATE SOURCE: Department of Hematology and Bone Marrow Transplantation, City of Hope National Medical Center, Duarte CA 91010, USA.

CONTRACT NUMBER: CA30206 (NCI)
CA33572 (NCI)
CA59308 (NCI)

SOURCE: BLOOD, (1996 Jul 15) 88 (2) 492-504.
Journal code: A8G; 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199609

ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 19970203
Entered Medline: 19960905

AB Gene transfer vectors based on adeno-associated virus (AAV) appear promising because of their high transduction frequencies regardless of cell cycle status and ability to integrate into chromosomal DNA. We tested AAV-mediated gene transfer into a panel of human bone marrow or umbilical cord-derived CD34+ hematopoietic progenitor cells, using vectors encoding several transgenes under the control of viral and cellular promoters. Gene transfer was evaluated by (1) chromosomal integration of vector sequences and (2) analysis of transgene expression. Southern hybridization and fluorescence in situ hybridization analysis of transduced CD34 genomic DNA showed the presence of integrated vector sequences in chromosomal DNA in a portion of transduced cells and showed that integrated vector sequences were replicated along with cellular DNA during mitosis. Transgene expression in transduced CD34 cells in suspension cultures and in myeloid colonies differentiating in vitro from transduced CD34 cells approximated that predicted by the multiplicity of transduction. This was true in CD34 cells from different donors, regardless of the transgene or selective pressure. Comparisons of CD34 cell transduction either before or after cytokine stimulation showed similar gene transfer frequencies. Our findings suggest that AAV transduction of CD34+ hematopoietic progenitor cells is efficient, can lead to stable integration in a population of transduced cells, and may therefore provide the basis for safe and efficient ex vivo gene therapy of the hematopoietic system.

L6 ANSWER 5 OF 7 BIOSIS

ACCESSION NUMBER: 199[redacted]53514 BIOSIS
DOCUMENT NUMBER: PRE[redacted]99799352717
TITLE: Modulation of chromosomal integration of adeno-associated virus vectors in CD34 cells.
AUTHOR(S): Guha, M.; **Fisher-Adams, G.; Wong., K. K., Jr.; Chatterjee, S.**
CORPORATE SOURCE: City Hope Natl. Med. Cent., Duarte, CA USA
SOURCE: Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 134A.
Meeting Info.: Thirty-eighth Annual Meeting of the American
Society of Hematology Orlando, Florida, USA December 6-10, 1996
ISSN: 0006-4971.
DOCUMENT TYPE: Conference; Abstract; Conference
LANGUAGE: English

L6 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:49333 BIOSIS
DOCUMENT NUMBER: PREV199698621468
TITLE: Stable integration of rAAV vector sequences into transformed and primary cells.
AUTHOR(S): **Fisher-Adams, G.; Wong., K. K., Jr.; Chatterjee, S.**
CORPORATE SOURCE: City Hope Natl. Med. Cent., Duarte, CA USA
SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 412A.
Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L6 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1996:49331 BIOSIS
DOCUMENT NUMBER: PREV199698621466
TITLE: Efficient transduction of primitive hematopoietic progenitor cells by adeno-associated virus vectors.
AUTHOR(S): **Chatterjee, S.**; Lu, D.; Shaughnessy, E.; **Fisher-Adams, G.**; Podsakoff, G.; Rossborough, E.; Li, L.; **Wong, K. K., Jr.**
CORPORATE SOURCE: City Hope Natl. Med. Cent., Duarte, CA USA
SOURCE: Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 412A.
Meeting Info.: 37th Annual Meeting of the American Society of Hematology Seattle, Washington, USA December 1-5, 1995
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 23:18:09 ON 13 JUL 2001
L1 20055 S (CHATTERJEE, ?)/IN,AU
L2 85570 S (WONG, ?)/IN,AU
L3 6617 S (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS, G?)
L4 112099 S L1 OR L2 OR L3
L5 13 S L1 AND L2 AND L3
L6 7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)

=> s l4 and (hematopoietic (3w) stem (3w) cell)

) IS NOT A RECOGNIZED COMMAND

The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> help commands

Enter one of these commands at the arrow prompt (=>).

ACTIVATE ----- Assign L#s to saved query or answer set.
ANALYZE ------ Build expand terms from answer fields.
ARCHIVE ------ Purchase rights for archiving.
DELETE ------- Delete saved or current session items.
DISPLAY ------ Display saved or current session items.
DUPLICATE ---- Determine duplicate answers
EDIT --------- Modify the text of an E-number entry.
EXPAND ------- Look at the index around a term.
FILE --------- Specify the search and display file.
FOCUS -------- Rank answers in order of relevancy.
FSEARCH ------ Find records from given patent family(s)
FSORT -------- Sort patent records by patent family
HELP --------- For help on how to use the system.
INDEX -------- Specify the Index environment.
LOGOFF ------- End the online session.
NEWS --------- Display current news about the system.
PRINT -------- Print answers offline.
REDISTRIBUTE - Purchase rights for redistribution.
SAVE --------- Save an L-numbered query or answer set.
SDI ---------- Request searches be run on file updates.
SEARCH ------- Perform a search.
SELECT ------- Build expand terms from answer fields.
SET ---------- Set terminal and interaction options.
SORT --------- Sort Answers of an L-number list
TABULATE ----- Analyze SmartSELECT L-number data.
TRANSFER ----- Extract terms from answers and search.
? ------------ The same as HELP.
Enter one of these commands at the arrow prompt (=>).

For more detailed information about a command, enter HELP followed by
the command name at an arrow prompt.

Example: => HELP SEARCH

For information on entering multiple commands at a single arrow
prompt, enter HELP COMMAND STACKING.

=> s l4 and (hematopoietic (3w) stem (3w) cell?)

   3 FILES SEARCHED...
L7   228 L4 AND (HEMATOPOIETIC (3W) STEM (3W) CELL?)

=> d his

     (FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001)

     FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 23:18:09 ON 13 JUL 2001
L1   20055 S (CHATTERJEE, ?)/IN,AU
L2   85570 S (WONG, ?)/IN,AU
L3   6617 S (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS,
G?)
L4   112099 S L1 OR L2 OR L3
L5   13 S L1 AND L2 AND L3
L6   7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)
L7   228 S L4 AND (HEMATOPOIETIC (3W) STEM (3W) CELL?)

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=> s l7 and g0

L8              8 L7 AND G0

=> duplicate remove l8

DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n

PROCESSING COMPLETED FOR L8
L9              4 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)

=> d ibib ab l9 1-4


L9   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:402018  CAPLUS
DOCUMENT NUMBER:          133:39105
TITLE:                    Transformation of very primitive quiescent human
                          hematopoietic stem cells
                          using adeno-associated virus vectors
INVENTOR(S):              Chatterjee, Saswati; Wong, Kamehameha K.,
                          Jr.; Wong, Christie Ann
PATENT ASSIGNEE(S):       City of Hope, USA
SOURCE:                   PCT Int. Appl., 56 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE          APPLICATION NO.  DATE
     ------------------  ----  --------      ---------------  --------
     WO 2000034495       A2    20000615      WO 1999-US28539  19991203
         W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
            CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
            IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
            MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
            SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,
            BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
            DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
            CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 1998-111017   P  19981204
AB   This invention relates to a method for transducing extremely primitive
     hematopoietic stem cells with high efficiency,
     using an adeno-assocd. vector.  This vector stably transforms highly
     primitive CD34+++CD38- cells which reside in a quiescent state and retain
     to a larger extent the ability to repopulate the hematopoietic system.

L9   ANSWER 2 OF 4  MEDLINE                                  DUPLICATE 1
ACCESSION NUMBER:   89062739      MEDLINE
DOCUMENT NUMBER:    89062739   PubMed ID: 3264195
TITLE:              Synergistic factors for stem cell proliferation: further
                    studies of the target stem cells and the mechanism of
                    stimulation by interleukin-1, interleukin-6, and
                    granulocyte colony-stimulating factor.
AUTHOR:             Ikebuchi K; Ihle J N; Hirai Y; Wong G G; Clark S
                    C; Ogawa M
CORPORATE SOURCE:   Department of Medicine, Medical University of South
                    Carolina, Charleston.
CONTRACT NUMBER:    AM32294 (NIADDK)
SOURCE:             BLOOD, (1988 Dec) 72 (6) 2007-14.
                    Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
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LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19890118

AB Serial observations of blast cell colony development from spleen cells of mice treated with 5-fluorouracil (5-FU) four days earlier revealed that either form of human interleukin-1 (IL-1 alpha or IL-1 beta) hastens the emergence of interleukin-3 (IL-3)-dependent blast cell colonies. This activity was essentially indistinguishable from the effect of interleukin-6 (IL-6) or granulocyte colony-stimulating factor (G-CSF) in the same system, an effect that we have ascribed previously to a shortening of the **G0** period of the dormant stem cells. We also analyzed the time courses of colony formation from cultures of day-2 post-5-FU marrow cells supported by IL-1 alpha, IL-6, or G-CSF alone or in combination with IL-3. In the presence of IL-3, G-CSF and IL-6 but not IL-1 alpha hastened the development of colonies and increased the numbers of multilineage colonies relative to cultures of IL-3 alone. This observation, together with our previous data from the human system, suggests that the synergistic effect of IL-1 is likely due to induction of secondary growth factors, including IL-6 and G-CSF, by accessory cells in culture. The effect of IL-6 on **G0** was confirmed by analysis of the cycling status of progenitor cells in short-term culture. While neither IL-3 nor IL-6 alone had any effect on the cycling status, the combination of factors resulted in a rapid recruitment of quiescent cells into cell cycle (within 48 hours) as represented by a twofold increase in the numbers of multipotential progenitors and a significant increase in the sensitivity of these cells to 3H-thymidine with high specific activity. Combinational testing of all of these synergistic factors revealed that the target cell populations for the IL-1, IL-6, and G-CSF overlap considerably, suggesting that they all may act through a common mechanism. This is further supported by our finding that cells from blast cell colonies grown in the presence of a combination of any one of the synergistic factors with IL-3 replate with higher efficiency and yield more multilineage secondary colonies than those from colonies grown in IL-3 alone. These findings provide further evidence that IL-1, IL-6, and G-CSF serve to integrate the immediate host responses to infection through augmentation of effector cells and antibody production as well as the longer term host responses by recruitment of dormant hemopoietic stem cells into active cell cycling.

L9 ANSWER 3 OF 4 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 88222419 MEDLINE
DOCUMENT NUMBER: 88222419 PubMed ID: 3259443
TITLE: Synergism between interleukin-6 and interleukin-3 in supporting proliferation of human **hematopoietic stem cells**: comparison with interleukin-1 alpha.
AUTHOR: Leary A G; Ikebuchi K; Hirai Y; **Wong G G**; Yang Y C; Clark S C; Ogawa M
CORPORATE SOURCE: VA Medical Center, Charleston, SC.
CONTRACT NUMBER: AM32294 (NIADDK)
SOURCE: BLOOD, (1988 Jun) 71 (6) 1759-63.
Journal code: A8G; 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198807
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880708

AB Currently available evidence suggests that in the steady state, the majority of **hematopoietic stem cells** are dormant in cell cycle and reside in the so-called **G0** period. Studies in our laboratory indicated that once a stem cell leaves **G0**, its subsequent proliferation requires the presence of interleukin-3 (IL-3). Recently it was reported that interleukin-1 (IL-1) may stimulate stem cells to become sensitive to IL-3. In a separate study, we observed that interleukin-6 (IL-6, also known as B cell stimulatory factor-2/interferon beta 2) possesses synergism with IL-3, shortening the **G0** period of murine **hematopoietic stem cells**. We report here that human IL-6 and IL-3 act synergistically in support of the proliferation of progenitors for human blast cell colonies and that IL-1 alpha reveals no synergism with IL-3 when tested against purified human marrow progenitors. Panned My-10+ human marrow cells were plated in culture and on day 14 of incubation, either IL-3, IL-6, IL-1 alpha or a combination of these factors was added to the cultures. Blast cell colony formation was analyzed daily between days 18 and 32 of culture. IL-6 or IL-1 alpha alone failed to support blast cell colony formation. In the presence of IL-3 alone, blast cell colonies continued to emerge between days 21 and 27. When a combination of IL-3 and IL-6 was added, blast cell colonies developed earlier than in cultures with IL-3 alone and twice as many blast cell colonies were identified. IL-1 alpha failed to augment IL-3-dependent blast cell colony formation. Replating studies of the individual blast cell colonies revealed various types of single as well as multilineage colonies. These observations suggest that IL-6 shortens the **G0** period of human **hematopoietic stem cells** and that the reported synergistic activities of IL-1 on primitive hematopoietic cells may be indirect.

L9 ANSWER 4 OF 4 MEDLINE
ACCESSION NUMBER: 88097422 MEDLINE
DOCUMENT NUMBER: 88097422 PubMed ID: 3501121
TITLE: Interleukin 6 enhancement of interleukin 3-dependent proliferation of multipotential hemopoietic progenitors.
AUTHOR: Ikebuchi K; **Wong G G**; Clark S C; Ihle J N; Hirai Y; Ogawa M
CORPORATE SOURCE: Medical University of South Carolina, Charleston.
CONTRACT NUMBER: AM32294 (NIADDK)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1987 Dec) 84 (24) 9035-9. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198802
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19880220

AB Interleukin-6 (IL-6, also known as B-cell stimulatory factor 2/interferon beta 2) was previously shown to support the proliferation of granulocyte/macrophage progenitors and indirectly support the formation of multilineage and blast cell colonies in cultures of spleen cells from normal mice. We report here that IL-3 and IL-6 act synergistically in support of the proliferation of murine multipotential progenitors in culture. The time course of total colony formation by spleen cells isolated from mice 4 days after injection of 5-fluorouracil (150 mg/kg) was significantly shortened in cultures containing both lymphokines relative to cultures supported by either of the two factors. Serial observations (mapping) of individual blast cell colonies in culture revealed that blast cell colonies emerged after random time intervals in the presence of IL-3. The average time of appearance in IL-6 alone was

somewhat delayed, [redacted]d in cultures containing both f[redacted]tors the appearance of multilineage bl[redacted]t cell colonies was significant[redacted] hastened relative to

cultures grown in the presence of the individual lymphokines. In cultures of day-2 post-5-fluorouracil bone marrow cells, IL-6 failed to support colony formation; IL-3 alone supported the formation of a few granulocyte/macrophage colonies, but the combination of factors acted synergistically to yield multilineage and a variety of other types of colonies. In this system, IL-1 alpha also acted synergistically with IL-3,

but the effect was smaller, and no multilineage colonies were seen. Together these results indicate that IL-3 and IL-6 act synergistically to support the proliferation of hemopoietic progenitors and that at least part of the effect results from a decrease in the G0 period of the individual stem cells.

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(FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 23:18:09 ON 13 JUL 2001

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L1        20055 S (CHATTERJEE, ?)/IN,AU
L2        85570 S (WONG, ?)/IN,AU
L3         6617 S (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS,
G?)
L4       112099 S L1 OR L2 OR L3
L5           13 S L1 AND L2 AND L3
L6            7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)
L7          228 S L4 AND (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L8            8 S L7 AND G0
L9            4 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)

=> s g0 (s) (hematopoietic (3w) stem (3w) cell?)

   3 FILES SEARCHED...
L10         124 G0 (S) (HEMATOPOIETIC (3W) STEM (3W) CELL?)

=> s l10 and (aav or (adenoassociated (3w) virus) or (adeno-associated (3w)
virus) or (adeno (3w) associated))

L11           1 L10 AND (AAV OR (ADENOASSOCIATED (3W) VIRUS) OR
(ADENO-ASSOCIATE
              D (3W) VIRUS) OR (ADENO (3W) ASSOCIATED))

=> d ibib ab l11

L11  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2000:402018  CAPLUS
DOCUMENT NUMBER:          133:39105
TITLE:                    Transformation of very primitive quiescent human
                          hematopoietic stem cells using adeno-
                          associated virus vectors
INVENTOR(S):              Chatterjee, Saswati; Wong, Kamehameha K., Jr.; Wong,
                          Christie Ann
PATENT ASSIGNEE(S):       City of Hope, USA
SOURCE:                   PCT Int. Appl., 56 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
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WO 2000034495 20000615 WO 1999-US285 19991203
    W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU,
       CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
       IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
       MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
       SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ,
       BY, KG, KZ, MD, RU, TJ, TM
    RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
       DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
       CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 1998-111017   P  19981204
AB  This invention relates to a method for transducing extremely primitive
    hematopoietic stem cells with high efficiency, using an adeno-assocd.
    vector.  This vector stably transforms highly primitive CD34+++CD38-
cells
    which reside in a quiescent state and retain to a larger extent the
    ability to repopulate the hematopoietic system.


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L3          6617 S (FISHER-ADAMS, G?)/IN,AU OR (FISHER, G?)/IN,AU OR (ADAMS,
G?)
L4        112099 S L1 OR L2 OR L3
L5            13 S L1 AND L2 AND L3
L6             7 DUPLICATE REMOVE L5 (6 DUPLICATES REMOVED)
L7           228 S L4 AND (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L8             8 S L7 AND G0
L9             4 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)
L10          124 S G0 (S) (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L11            1 S L10 AND (AAV OR (ADENOASSOCIATED (3W) VIRUS) OR
(ADENO-ASSOCI

=> s l10 and adenovirus

L12            0 L10 AND ADENOVIRUS

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    (FILE 'HOME' ENTERED AT 23:17:49 ON 13 JUL 2001)

    FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 23:18:09 ON 13 JUL 2001
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L8             8 S L7 AND G0
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L10          124 S G0 (S) (HEMATOPOIETIC (3W) STEM (3W) CELL?)
L11            1 S L10 AND (AAV OR (ADENOASSOCIATED (3W) VIRUS) OR
(ADENO-ASSOCI
L12            0 S L10 AND ADENOVIRUS

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	67.56	67.71
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.76	-1.76

STN INTERNATIONAL LOGOFF AT 23:29:48 ON 13 JUL 2001